Fetal Growth and Hyperinsulinaemia in Adult Life

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To explore the relation between reduced fetal growth and impaired glucose tolerance in adult life, an oral glucose tolerance test (75 g glucose) was carried out on 218 men and women, now aged around 50 years, who had been measured in detail at birth. Measurements of plasma concentrations of glucose and insulin were made at 0, 30, and 120 min. Fasting plasma concentrations of proinsulin and 32-33 split proinsulin were also measured. People in the highest category of birthweight tended to have the lowest plasma concentrations of insulin as adults at both 0 and 120 min, though both these relations were weak. Plasma insulin concentrations in adult life were more strongly related to abdominal circumference at birth than to birthweight. After adjusting for sex and body mass index, mean insulin concentrations at 0 min fell from 50 pmol l^{-1} to 46 pmol l^{-1} ($p = 0.04$) and at 120 min from 235 pmol l^{-1} to 144 pmol l^{-1} ($p = 0.003$) between people whose abdominal circumference at birth had been less than 11.5 in and those who abdominal circumference had been greater than 13 in. Plasma glucose concentrations at 120 min also fell with increasing abdominal circumference at birth. Because abdominal circumference at birth is an indicator of the growth of the liver in fetal life, one interpretation of these findings is that the sensitivity of the liver to insulin is permanently reduced if the intrauterine development of this organ is impaired. © **1998 John Wiley & Sons, Ltd.**

***Diabet. Med.* 15: 688–694 (1998)**

KEY WORDS **fetal growth; insulin resistance; diabetes mellitus; liver**

Received 3 December 1997; revised 24 March 1998; accepted 29 March 1998

Introduction

There is now evidence from several studies that low birthweight is associated with increased risk of impaired glucose tolerance and diabetes in adult life.[1–5] The processes that underlie this link are unknown. One possibility is that impaired growth of the endocrine pancreas during early development results in permanent reduction in the pancreatic complement of β cells and a diminished capacity for insulin secretion. In experimental animals, a brief period of protein-calorie malnutrition in early life leads to a permanent impairment of the insulin response to glucose.[6] A second possibility is that people who were small at birth are relatively insulin resistant as adults. While these hypotheses are not mutually exclusive, the results of studies of middle-aged men and women of known birth measurements suggest that the second may be more important. In these people, rate of fall of blood glucose concentrations after intraveneous injection of insulin—an index of insulin resistance—was slower in those who were light or thin at birth.[7] By contrast, first phase insulin secretion following an intravenous glucose tolerance test was not related to measurements of prenatal growth.[8] These findings suggest that adaptations made by skeletal muscle or the liver, both important sites of insulin resistance, in response to a period of impaired fetal growth permanently affect the sensitivity of these tissues to insulin.

We have studied a group of men and women, now aged around 50 years, who were born in the Jessop Hospital for Women, Sheffield, UK and whose birth records are available. In the past, all babies born in this hospital were measured in detail, including their abdominal circumference, an indicator of the growth of the liver in fetal life. This provided an opportunity to investigate the relation between the development of this organ and adult glucose tolerance.

Patients and Methods

A standard form was used to record details of mother and baby for each admission to the Jessop Hospital for Women, Sheffield. The information recorded included the date of the mother's last menstrual period and pelvimetry. The baby's birthweight was recorded in both pounds and grammes. Its head, chest and abdominal circumferences were recorded in inches. The weight of

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Sponsors: Medical Research Council; Wellcome Trust; Children Nationwide

 CCC 0742–3071/98/080688–07$17.50

the placenta was recorded in grammes. No information was available about growth during infancy.

We used the National Health Service Central Register to trace 1039 singleton infants born in the hospital to married mothers during 1939–40 and whose records were complete. Four hundred and nineteen were still living in Sheffield. After obtaining permission from their general practitioners, we wrote to them asking if we might visit and interview them in their homes. Three hundred and thirty-seven (80 %) agreed and were seen by one of four fieldworkers. The fieldworker, who had not seen the data concerning the person's birth, administered a questionnaire which inquired about smoking habits, alcohol consumption, current occupation, and father's occupation. No attempt was made to collect information about familial incidence of diabetes or other diseases. Height was measured with a portable stadiometer and weight with a portable Seca scale and waist and hip circumference with tape measures. The subject's social class at birth was defined from their father's occupation and current social class derived from their own or their husband's occupation. Before starting the study, the procedures for taking all measurements were standardized and the fieldworkers trained. After the training period, a check, in which repeated measurements were made on subjects selected from outside the study population, revealed no significant interobserver variation.

After the interview subjects were asked to attend a clinic at the Northern General Hospital, Sheffield after an overnight fast; 235 agreed to do so. Six subjects known to have diabetes were excluded. A standard 75 g oral glucose tolerance test was successfully performed on 218 subjects. Plasma glucose and insulin concentrations at 0, 30, and 120 min and proinsulin and 32-33 split proinsulin concentrations at zero time only were measured. All the participants in the study were white Caucasians.

Plasma glucose was measured by a hexokinase method. Plasma insulin, proinsulin and 32-33 split proinsulin concentration were determined by two site immunometric assays with iodine-125 or alkaline phosphatase as labels. The insulin assay was standardized against the first international reference preparation coded 66/304 and the intact and split proinsulin assays against standards obtained from Lilly Research Laboratories (Indianapolis, USA). Diabetes mellitus and impaired glucose tolerance were defined according to standard criteria.[9] The South Sheffield Ethics Committee gave its approval for this study.

Statistical Analysis

Multiple linear regression and tabulation of means were used to examine the relation between maternal measurements and measurements of the baby at birth and adult plasma concentrations of glucose, insulin and intact and 32-33 split proinsulin. The frequency distributions of plasma concentrations of both glucose and insulins were skewed and logarithmic transformations were used to normalize them. Birthweight was divided into groups as in our previous studies.[1,2] Categories of abdominal circumference were chosen so that there were approximately the same number of babies in each of the four groups.[10] For clarity of presentation, we have shown the results as tables of mean values of plasma concentrations of glucose and insulin within each group of birth measurements. In the tables, mean concentrations have been transformed back to the original units of measurement and they therefore represent geometric means. All values given for statistical significance were calculated by regression using maternal and birth measurements as continuous rather than categorical variables.

Results

Out of 218 people who completed a 2 h oral glucose tolerance test, 32 (21 men, 11 women) had impaired glucose tolerance and 4 (3 men, 1 women) had diabetes. On average, men with impaired glucose tolerance or diabetes were heavier and had a higher body mass index, defined as weight(kg)/height^2(m), than those with normal glucose tolerance. These differences were not present amongst women. There were no statistically significant differences in any birth measurement between those with impaired glucose tolerance or diabetes and those without, in either men or women (Table 1). Nor were there any statistically significant differences in birth measurements between those who completed the glucose tolerance test and those who were excluded or declined to take part.

Plasma concentrations of glucose, both fasting and during an oral glucose tolerance test, were higher in men than women. Geometric mean fasting glucose concentrations in men were 5.87 mmol l^{-1} and in women 5.41 mmol l^{-1} ($p < 0.001$). Corresponding values for insulin were 49.9 pmol l^{-1} and 44.2 pmol l^{-1} ($p = 0.1$). Geometric mean concentrations of glucose at 120 min in men were 6.57 mmol l^{-1} and in women 6.06 mmol l^{-1} ($p = 0.04$). Corresponding values for insulin were 165.6 pmol l^{-1} and 189.6 pmol l^{-1} ($p = 0.2$).

Plasma concentrations of glucose and insulin tended to be higher in people with a greater body mass index or a larger waist/hip ratio. In a regression analysis, fasting concentrations of glucose and insulin increased by 2 % (p for trend = 0.07) and 34 % (p for trend < 0.001), respectively, for each standard deviation increase in body mass index and by 4 % (p for trend = 0.1) and 32 % (p for trend < 0.001), respectively, for each standard deviation increase in waist/hip ratio. At 120 min, concentrations of glucose and insulin increased by 5 % (p for trend < 0.01) and 29 % (p for trend < 0.001), respectively, for each standard deviation increase in body mass index and by 8 % (p for trend < 0.01) and 42 % (p for trend < 0.001), respectively, for each standard deviation increase in waist/hip ratio. Birthweight was

Table 1. Mean body size, currently and at birth, between those with and without impaired glucose tolerance or diabetes mellitus

	Men					Women				
	Impaired glucose tolerance or diabetes mellitus ($n = 24$)	No impaired glucose tolerance ($n = 88$)	Difference (with – without)	95 % CI	p	Impaired glucose tolerance or diabetes mellitus ($n = 12$)	No impaired glucose tolerance ($n = 94$)	Difference (with – without)	95 % CI	p
Age (yr)	52.2	52.1	0.13	–0.16 to 0.41	0.4	52.2	52.2	0.02	–0.35 to 0.39	0.9
Height (cm)	172.9	172.6	0.27	–2.85 to 3.40	0.9	160.3	160.8	–0.51	–3.95 to 2.93	0.8
Weight (kg)	86.1	79.2	6.88	1.22 to 12.54	0.02	68.1	69.5	–1.36	–9.91 to 7.19	0.8
BMI (kg m^{-2})	28.8	26.6	2.23	0.55 to 3.91	0.001	26.4	26.9	–0.44	–3.72 to 2.85	0.8
Waist/hip ratio	0.95	0.92	0.02	–0.001 to 0.050	0.07	0.78	0.78	0.01	–0.97 to 1.04	0.7
Birthweight (oz)	119.5	114.4	5.14	–3.54 to 13.83	0.2	108.9	113.5	–4.60	–14.45 to 5.24	0.4
Length at birth (in)	20.1	19.8	0.31	–0.17 to 0.79	0.2	19.8	19.9	–0.12	–0.71 to 0.45	0.7
Abdominal circumference at birth (in)	12.1	12.4	–0.26	–0.80 to 0.28	0.3	12.3	12.4	–0.13	–0.76 to 0.51	0.7
Head circumference at birth (in)	13.7	13.6	0.06	–0.25 to 0.38	0.7	13.4	13.4	–0.01	–0.38 to 0.36	0.9
Head to length ratio at birth	0.68	0.69	–0.01	–0.97 to 1.01	0.2	0.68	0.67	0.00	–0.02 to 0.02	0.8
Ponderal index at birth (kg m^{-3})	25.44	25.38	0.06	–1.27 to 1.39	0.9	24.2	24.8	–0.63	–2.41 to 1.15	0.5

weakly related to body mass index in adult life ($p = 0.03$) but not to waist/hip ratio. No other birth measurement was related to either body mass index or to waist/hip ratio.

There were no statistically significant relations between insulin or glucose concentrations and either external conjugate or inter-cristal diameter of the mother's pelvis; placental weight; head and chest circumferences at birth; ponderal index at birth or gestational age at birth. Neither were they related to social class at birth or currently, nor to subjects' smoking habit or alcohol consumption. Plasma concentrations of the insulin precursors, proinsulin and 32-33 split proinsulin were not significantly related to any birth measurement. Within the narrow age range of the subjects in the study there was no relation between concentrations of insulin, proinsulin, 32-33 split proinsulin or glucose, and age.

Glucose and insulin concentrations at 30 min during the oral glucose tolerance test were not statistically significantly related to any birth measurement. However, people who had been light at birth tended to have higher plasma concentrations of insulin and glucose both fasting and at 120 min. These relations, however, were weak and, even after adjustment for sex and body mass index, only the inverse relation between birthweight and fasting plasma insulin concentrations was statistically significant ($p = 0.01$). Mean plasma concentrations of glucose and insulin according to five categories of birthweight are shown in Table 2.

Plasma concentrations of glucose and insulin were more strongly related to abdominal circumference at birth than to birthweight. Table 3 shows that, after adjustment for sex and current body mass index, mean fasting insulin concentrations fell from 51 pmol l^{-1} in people whose abdominal circumference at birth had been less than 11.5 in to 42 pmol l^{-1} in those whose abdominal circumference had been greater than 13 in (p for trend = 0.04). Mean glucose concentrations at 120 min fell from 6.6 mmol l^{-1} in people whose abdominal circumference at birth had been less than 11.5 in to 6.0 mmol l^{-1} in those whose abdominal circumference had been greater than 13 in (p for trend = 0.04). The corresponding insulin concentrations at 120 min were 235 pmol l^{-1} and 144 pmol l^{-1}, respectively (p for trend = 0.003). Figure 1 shows a scattergram and regression analysis of the relation between abdominal circumference at birth and plasma insulin concentration at 120 min after adjustment for sex and current body mass index.

To examine the relative strength of the effects of adult obesity and size at birth on glucose and insulin concentrations, we included birthweight, abdominal circumference at birth, sex, current body mass index, and current waist/hip ratio in a multiple regression model. In this model, only the effects of sex, abdominal circumference at birth and current body mass index were statistically significant; plasma glucose concentrations increased by 7 % (95 % CI 2 to 11 %) for each standard deviation decrease in abdominal circumference at birth and by 3 % (95 % CI −1 to 7 %) for each standard deviation increase in current body mass index. Plasma insulin concentrations increased by 18 % (95 % CI 4 to 29 %) for each standard deviation decrease in abdominal circumference at birth and by 23 % (95 % CI 9 to 38 %) for each standard deviation increase in current body mass index.

When the sexes were analysed separately, the relations described above, and summarized in Tables 2 and 3, were stronger in men than in women. The relations between birthweight and fasting insulin concentrations and between abdominal circumference at birth and fasting and 120 min insulin concentrations remain statistically significant when the data for men, but not for women, are analysed alone. However, interaction terms for sex and birthweight or sex and abdominal circumference at birth are not statistically significant in a multiple regression model. The evidence is insufficient to support a sex difference in these data.

Discussion

In this group of men and women aged around 50 years, there are consistent trends of increasing plasma insulin concentrations, both fasting and during an oral glucose tolerance test, with decreasing birthweight and with decreasing abdominal circumference at birth. No other birth measurement was related to insulin concentrations. Plasma concentrations of glucose also tended to rise as abdominal circumference at birth fell, but the relations were weaker than those with insulin.

The subjects in this study were born in hospital at a time when many births took place at home. They have also continued to live in the city in which they were born and they cannot therefore be considered representative of all people born in Sheffield. However, our analyses are based on comparisons within the sample. Unless the relations between concentrations of insulin and glucose and fetal growth differ between people born at home and people born in hospital or between migrants and non-migrants, no bias will have been introduced. The associations between measurements made at birth and plasma concentrations were independent of variables associated with adult lifestyle, including social class, cigarette smoking, and alcohol consumption.

The trends of rising plasma concentrations of insulin and glucose with decreasing birthweight, although statistically less strong than in some earlier studies, is in keeping with their findings. The fact that both glucose and insulin concentrations tend to be raised in adults who were small at birth is consistent with the suggestion that impaired fetal growth leads to an increase in insulin resistance. The new finding in this study is the relation of glucose and insulin concentrations with abdominal circumference at birth. Abdominal circumference at birth is a measure of the growth of the liver during fetal life.[11] We suggest that the association of increased plasma insulin concentrations with reduced abdominal circum-

Table 2. Geometric mean plasma concentrations of glucose and insulin (unadjusted and adjusted for sex and current BMI) at 0 and 120 min during an oral glucose tolerance test according to birthweight

Birthweight (lb)	Fasting				At 120 min during an oral glucose tolerance test				*n*
	Glucose (mmol l^{-1})		Insulin (pmol l^{-1})		Glucose (mmol l^{-1})		Insulin (pmol l^{-1})		
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	
≤ 5.5	5.7	5.7	44	46	6.6	6.6	209	220	11
5.6 – 6.5	5.6	5.6	48	53	6.0	6.1	188	202	45
6.6 – 7.5	5.6	5.6	46	46	6.0	5.9	165	166	96
7.6 – 8.5	5.6	5.6	51	48	6.3	6.2	190	182	59
> 8.5	5.5	5.4	42	36	6.2	6.0	139	128	17
Significance of trend	$p = 0.7$	$p = 0.7$	$p = 0.4$	$p = 0.01$	$p = 0.6$	$p = 0.9$	$p = 0.4$	$p = 0.1$	218

Table 3. Geometric mean plasma concentrations of glucose and insulin (unadjusted and adjusted for sex and current BMI) at 0 and 120 min during an oral glucose tolerance test according to abdominal circumference at birth

Abdominal circumference (in)	Fasting				At 120 min during an oral glucose tolerance test				*n*
	Glucose (mmol l^{-1})		Insulin (pmol l^{-1})		Glucose (mmol l^{-1})		Insulin (pmol l^{-1})		
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	
≤ 11.5	5.7	5.7	50	51	6.6	6.6	230	235	52
11.6 – 12.25	5.6	5.6	45	47	5.8	5.9	159	166	47
12.26 – 13	5.6	5.6	47	47	6.0	6.0	167	167	74
> 13	5.6	5.6	46	42	6.1	6.0	155	144	43
Significance of trend	$p = 0.9$	$p = 0.8$	$p = 0.3$	$p = 0.04$	$p = 0.07$	$p = 0.04$	$p = 0.01$	$p = 0.003$	216[a]

[a]Information on abdominal circumference at birth was missing for 2 subjects.

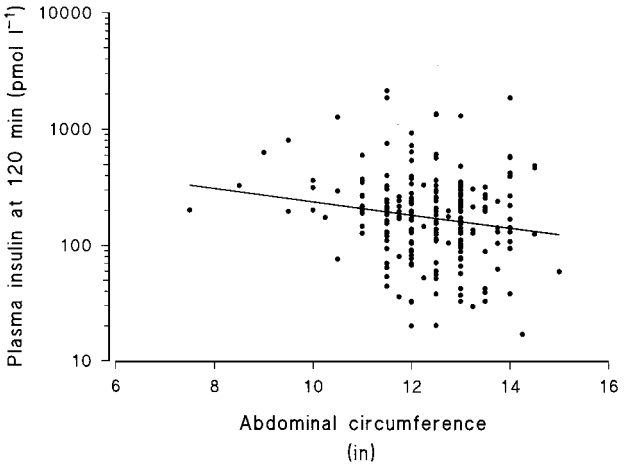

Figure 1. Plasma insulin concentrations, adjusted for sex and current body mass index, at 120 min in a glucose tolerance test in 216 men and women according to abdominal circumference at birth. An increase of 1 in in abdominal circumference is associated with a 14 % fall in plasma insulin concentration (95 % confidence interval: 5 to 22 %; $r = -0.17$, $p < 0.01$)

ference at birth may indicate that the liver's sensitivity to insulin is permanently influenced by how the organ develops before birth. Further evidence that impaired growth of the liver during fetal development can have long-term consequences for the metabolism of the adult organism derives from findings that reduced abdominal circumference at birth is associated with raised plasma concentrations of fibrinogen and LDL cholesterol in adult life.[12,13]

There are however, some differences between the results described in this paper and the findings of earlier investigations. In a group of 266 men and women born in Preston, Lancashire, UK and aged between 46 and 54 years at the time they were studied, impaired glucose tolerance and plasma concentrations of insulin and glucose were related to thinness and shortness at birth.[2] In a study in Sweden, thinness at birth was strongly associated with both risk of diabetes and insulin concentrations.[5] We found no similar relation in the present study. Thinness at birth, as indicated by a low ponderal index (birthweight/length^3), is thought to be an indication of a reduction in rate of fetal growth in the mid trimester of pregnancy. We wondered if the reason for the lack of a relation between impaired glucose tolerance and low ponderal index in Sheffield was simply that few subjects in Sheffield suffered from this pattern of impairment of fetal growth. Comparison of birth measurements in the two towns shows that while babies born in Sheffield were, on average, heavier at birth and had larger heads, they were shorter than babies born in Preston. The mean ponderal index of the Sheffield babies in this study was 25.1 kg m^{-3} as compared with 22.8 kg m^{-3} in the Preston babies. But this explanation cannot account for the differences between our results and those of the Swedish study where mean ponderal index was around 26.5 kg m^{-3}. However, the Swedish study was considerably larger and therefore statistically more powerful and used a different indicator of insulin resistance—an intravenous glucose tolerance test.

The results presented here differ from those of the study in Preston in another respect. In Preston, impaired glucose tolerance was related to the ratio of birthweight to placental weight. No such relation was found in this study (data not shown). However, because undernutrition in pregnancy may either constrain or stimulate placental growth, depending upon its timing and severity, the associations between placental size and glucose tolerance are likely to vary from one population to another.

It is possible that several mechanisms link reduced fetal growth with hyperinsulinaemia or impaired glucose tolerance in adult life, and that their relative importance varies between individuals and between populations. An interpretation of the results presented here is that one of the mechanisms involves a re-setting of hepatic insulin sensitivity. This hypothesis can be tested by measuring the sensitivity of hepatic glucose output to suppression by insulin in people whose early growth was recorded.

Acknowledgements

We are grateful to all the men and women who gave their time to participate in the study, to the medical records department at the Jessop Hospital for Women, Sheffield who preserved the records and allowed us to use them, to the staff of the NHS Central Register, Southport and the Sheffield Family Health Services Authority who helped locate the subjects, and to N. Read who allowed us to hold clinics in his department. K. Ellis, C. Laughton, R. Strong, and C. Williams carried out the fieldwork. G. Wield was responsible for data processing. The study was funded by the Medical Research Council, the Wellcome Trust, and Children Nationwide.

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